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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
06267.0126-00000

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Signature _____

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Application Number	Filed
10/537,622	**March 29, 2006**

First Named Inventor
Tomi JARVINEN

Art Unit	Examiner
1626	**L. STOCKTON**

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.

■ attorney or agent of record.
Registration number **60,974**.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Erin M. Sommers
Signature

Erin M. Sommers
Typed or printed name

202-408-4292
Telephone number

February 17, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

■ *Total of 5 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Claims 1, 4, and 7-10 are currently pending and stand rejected. Claims 1, 4, and 7-10 stand rejected under 35 U.S.C. § 103(a) as obvious over WO 97/12874 ("WO '874") and U.S. Patent No. 6,313,311 ("Karjalainen") each taken alone or in view of WO 01/051472 ("WO '472"), Bundgaard, H. *Drugs of the Future* (1991) 16(5):443-458 ("Bundgaard I"), U.S. Patent No. 4,673,679 ("Aungst"), and Krogsgaard-Bundgaard, H., "Chapter 5. Design and Application of Prodrugs" in *A Textbook of Drug Design and Development* (1991), Harwood Academic Publishers, Philadelphia, pp. 112-191 ("Bundgaard II").[1] Final Office Action dated October 19, 2009 ("OA"), page 14. Applicants respectfully disagree with and traverse this rejection.

The Office has not established a *prima facie* case of obviousness because there would have been no reason to modify the cited art to arrive at the presently recited inventions, and the cited art fails to support a reasonable expectation of success that the instantly claimed compounds would have worked for their intended purpose. *Takeda Chem. Ind., Ltd. v. Alphapharm PTY Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). The obviousness inquiry is not, as suggested during the interview, whether the skilled artisan possibly could have envisioned the claimed invention but, rather, whether a skilled artisan would have been led to the invention and had a reasonable expectation of success. *See In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962).

Even if a skilled artisan could have envisioned a pivaloyl ester within the compounds disclosed in the art, to establish a *prima facie* case of obvious from such a disclosure, after *KSR Int'l Co. v. Teleflex Inc.* 127 S. Ct. 1727 (2007), "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish

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[1] The '311 patent is a § 371 continuation of the International Application that published as WO '874. The specifications of the two documents are the same. Accordingly, Applicants refer to only the '311 patent herein.

prima facie obviousness of a new claimed compound." *Takeda*, 492 F.3d at 1357. In the present case, no such reason exists.

Neither WO '874 nor Karjalainen discloses pivaloyl esters. Rather, each states "[t]ypical esters include the lower alkyl esters, such as the methyl, ethyl and propyl esters." WO '874, page 4, lines 27-28; Karjalainen, col. 3, lines 46-47. WO '472 also fails to disclose pivaloyl esters: "Examples of esters include esters of aliphatic or aromatic alcohols, e.g., lower alkyl esters, e.g., methyl, ethyl and propyl." Page 8. Bundgaard I and II (drawn to prodrugs) also do not disclose pivaloyl esters. Finally, as discussed in detail below, Aungst would have discouraged a skilled artisan from choosing a pivaloyl ester as a prodrug form.

According to Bundgaard II (page 116), the rational design of prodrugs "requires that the underlying causes which necessitate or stimulate the use of the prodrug approach be defined and clearly understood." Indeed, "[p]rodrugs are designed to overcome pharmaceutically and/or pharmacokinetically based problems associated with the parent drug molecule that would otherwise limit the clinical usefulness of the drug." Bundgaard II, page 115. But none of the cited art even contemplates that the parent drug 4-(6-hydroxyindan-1-ylmethyl)-1*H*-imidazol-1-ium chloride has any pharmaceutically or pharmacokinetically disadvantageous properties. In fact, according to Karjalainen, the parent drug showed favorable binding activity and selectivity. Karjalainen, cols. 11-12, "Test Results," (Example 2).[2] As a result, even an obvious-to-try standard would not support a *prima facie* case of obviousness because "there was no design need or market pressure to solve a problem." *KSR*, 127 S. Ct. at 1742. Absent a cognizable problem, there would have been no reason to modify Karjalainen to arrive at the presently pending claims.

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[2] 3-(1*H*-imidazol-4-ylmethyl)-indan-5-ol chloride is the same as 4-(6-hydroxyindan-1-ylmethyl)-1*H*-imidazol-1-ium chloride.

Moreover, the present case is not like that in *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), where the court invalidated claims to a besylate salt as obvious. In *Pfizer*, the art disclosed a broad genus that included "acid addition salts to improve bioavailability." Although the besylate salt was not specifically mentioned, other cited art expressly trumpeted the superiority of besylate salts. Consequently, the Court concluded that, based on the teachings in the art, a skilled artisan would have been led to the claimed besylate salt with a reasonable expectation of success.

In contrast to *Pfizer*, the documents cited by the Office provide no motivation or expectation of success—they do not suggest that the bioavailability or any other pharmaceutical property of 4-(6-hydroxyindan-1-ylmethyl)-1*H*-imidazol-1-ium chloride needs to be improved. Nor do they suggest that the pivaloyl ester would be a well known solution to any such problem. Rather, as mentioned above, Bundgaard I and II do not even disclose a pivaloyl ester as a potential prodrug, and Aungst would have discouraged a skilled artisan from choosing the pivaloyl ester because the disclosed pivaloyl ester 1) is barely hydrolyzed in human plasma (Table 1, less than 10% hydrolysis in 24 hours), 2) is less or equally bioavailable as its free forms (Table 7, naloxone and naltrexone), and 3) the pivalate of nalbuphine is less bioavailable than other pro-drugs. Aungst, Table 7 (compare pivalate to salicylate and acetylsalicylate). Thus, unlike the art in *Pfizer* where there was a clear preference for the superior besylate salt, Aungst suggests the undesirability of a pivaloyl ester, albeit for different base compounds than the one presently claimed.

Furthermore, Bundgaard I and II emphasize the unpredictability of selecting a suitable prodrug, undermining a skilled artisan's expectation of success. No single ester—or other functional group for that matter—is universally suitable for all potential prodrug applications.

For example, Bundgaard I (p. 444) explains that "many aliphatic or aromatic esters are not sufficiently labile *in vivo* to ensure a sufficiently high rate and extent of prodrug conversion." In a specific example, the simple alkyl and aryl esters of penicillin are not hydrolyzed to the active free penicillin *in vivo* and, as a result, have no pharmaceutical value. *Id.* Indeed, Bundgaard II (p. 153) suggests that *in vivo* hydrolysis of ester prodrugs fits no standard formula:

> While the chemical reactivity of esters is readily predictable on the basis of the steric and electronic properties of the substitutes in both the acyl and alcohol moieties, this ***does not apply*** for the enzymatic hydrolysis. Steric effects generally alter non-enzymatic and enzymatic ester hydrolysis rates in the same direction, but exceptions exist. For enzymatic ester hydrolysis the hydrophilic property and charge of the ester may play a major role and non-enzymatic hydrolysis cannot be used as a reliable guide to enzyme-catalysed reactions.

(Emphasis added). The unpredictability of prodrug chemistry disclosed in Bundgaard I and II, and the disappointing performance of the pivalate ester in Aungst not only fail to motivate the skilled artisan but also dampens her expectation of success.

It is only with Applicants' own disclosure that the advantageous properties of the recited compounds is shown. To insist, as the Examiner did in a voicemail to Applicants' representatives, that the improved bioavailability (Table 1) and duration of pharmacological action (Experiment 4) compared to the parent drug is doing no more than what one of ordinary skill in the art would expect for a prodrug, impermissibly imports hindsight into the obviousness analysis. *In re Dow Chem. Co. v. Am. Cyanamid Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("There must be a reason or suggestion in the art for selecting the procedure used, *other than* the knowledge learned from the applicant's disclosure.") (Emphasis added); *see also* M.P.E.P. § 2142 ("[I]mpermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art."). To use "that which the inventor taught against its teacher," especially when the art of record teaches away from using a pivalate ester, bolsters

the non-obviousness of the present claims. Because no reason exists to modify the prior art, and the skilled artisan would have had limited expectation of success, no *prima facie* case of obviousness has been established. Thus, this rejection should be withdrawn.

Claims 1, 4, and 7-10 also stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 5, 6, 8, 14, and 16-24 of Karjalainen. OA at 3. Claims 7 and 8 were provisionally rejected on the same ground over claims 15, 16, 19, 24, and 27-32 of U.S. Patent Application No. 11/641,953. OA at 11. Applicants respectfully disagree with and traverse these rejections.

As clearly stated in the M.P.E.P.,

> **Domination and double patenting should not be confused.** They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. **Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection**.

M.P.E.P. § 804(II) (*citing In re Kaplan,* 789 F.2d 1574, 1577-78 (Fed. Cir. 1986); and *In re Sarrett*, 327 F.2d 1005, (CCPA 1964)) (emphasis added).

Thus, even if the claimed inventions fall within the literal scope of the claims of the cited art, that fact alone does not establish obviousness-type double patenting. Rather, to support such a rejection, the claims of the cited art must have rendered the present claims obvious. Applicants assert that they do not for at least the reasons discussed above with respect to the obviousness rejections. Accordingly, Applicants respectfully request the withdrawal of the obviousness-type double patenting rejections.